Tailoring the mechanical and biological properties of 3D-printable granular hydrogels

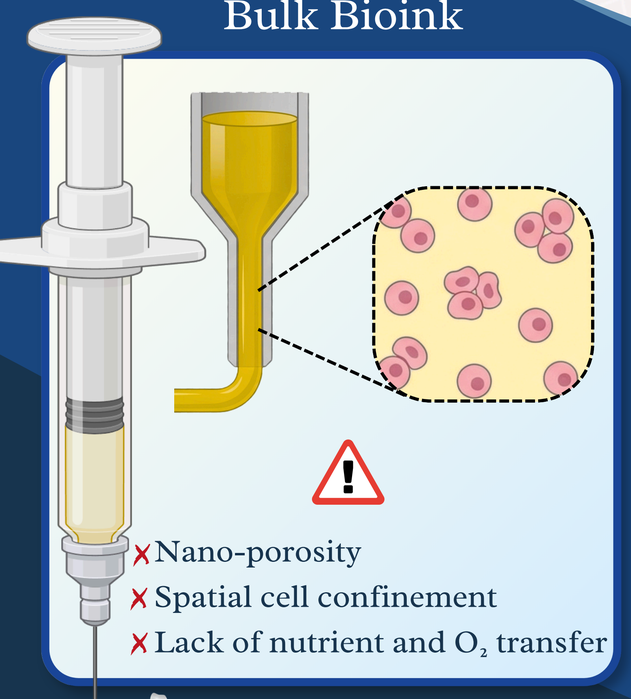
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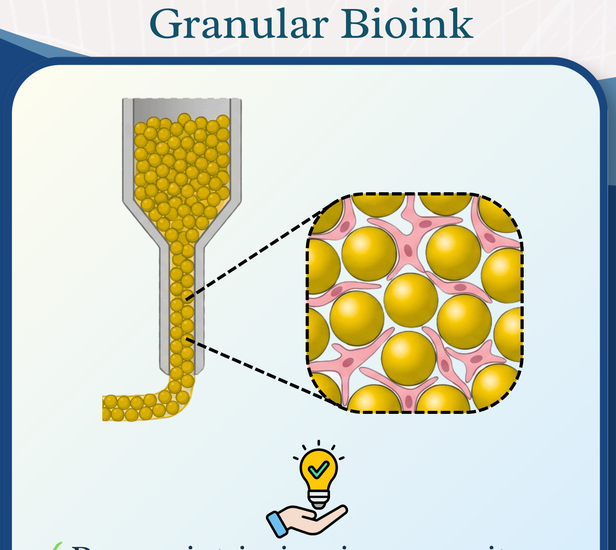
Introduction

Bulk Bioink



✗ Nano-porosity
✗ Spatial cell confinement
✗ Lack of nutrient and O_2 transfer

Granular Bioink

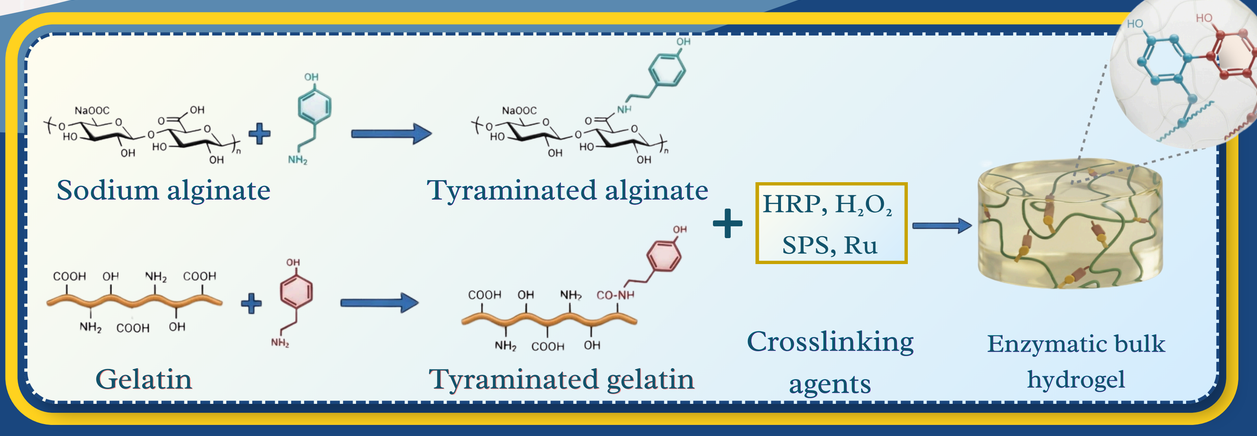


✓ Possess intrinsic micro-porosity
✓ Superior biological functionality
✓ Excellent shear-thinning properties

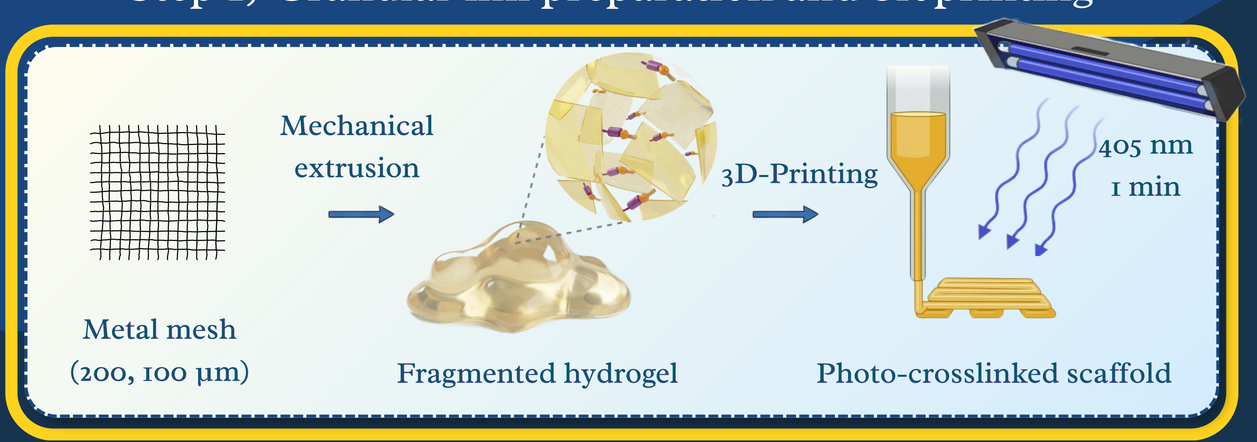
Our focus is to understand how balancing inter- and intra-particle crosslinking, alongside interstitial void fraction, influences the printability, mechanical and biological behavior.

Methodology

Step 1) Polymer functionalization and gel formation



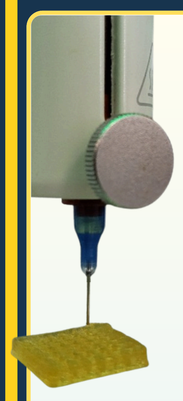
Step 2) Granular ink preparation and bioprinting

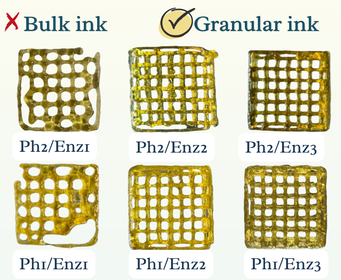


Results and discussion

Intra- and inter-particle crosslinking → Interstitial void fraction → Biological functionality

Shape fidelity



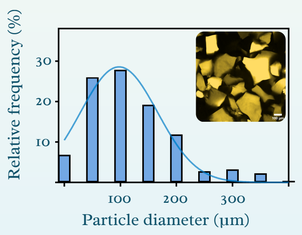


Enzymatic agents

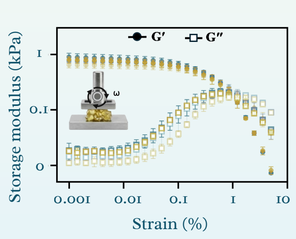
HRP/H_2O_2 (Unit.mL^{-1}/ mM)	
Enz1	2.5/0.5
Enz2	5/3
Enz3	7.5/4.5

Photoinitiators

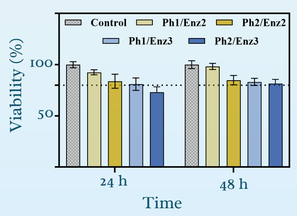
Ru/SPS (mM)	
Ph1	0.25/2.5
Ph2	0.5/5



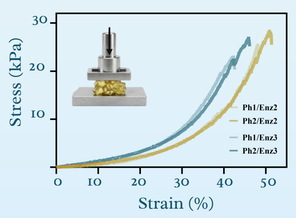
Irregular microparticles, in the range of (10-350) µm



Shear thininng properties; suitable for extrusion-based printing



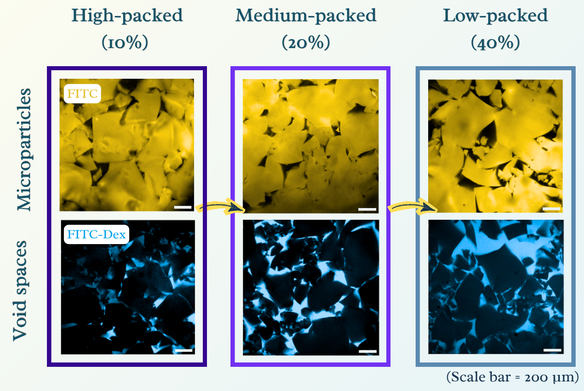
Non-toxic crosslinking agents concentrations



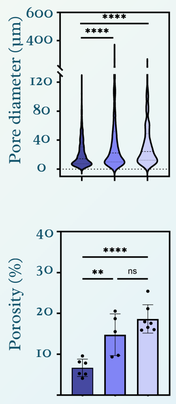
Compressive strength up to ~25 kPa; comparable to bulk counterparts!

Considering both mechanical properties and cytotoxicity, Ph1/Enz2 was selected as the lowest effective concentration for granular ink formation.

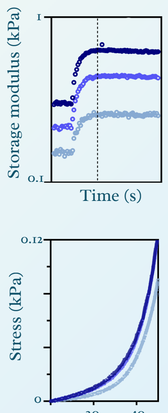
Microparticle packing density



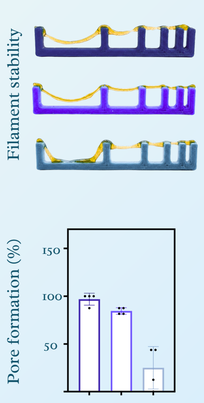
Pore characteristics



Mechanical strength



Ink printability

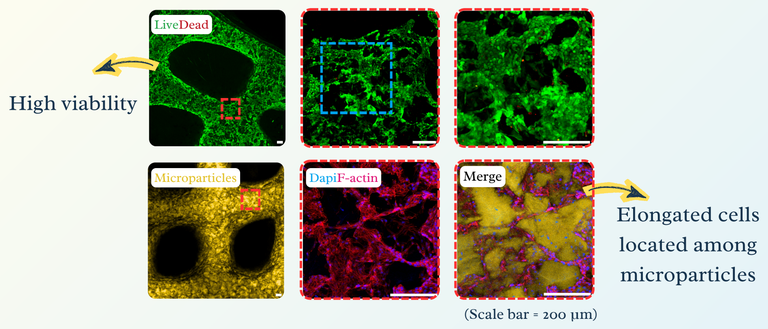


Higher packing density:

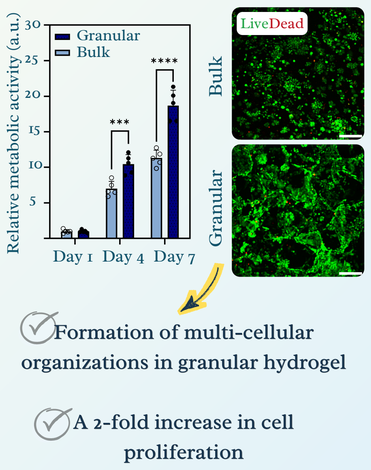
↓ Porosity degree ↑ Stiffness ↑ Shape fidelity

Medium-packed is opted as the optimized packing density.

L929 Bioprinting (Day 7)



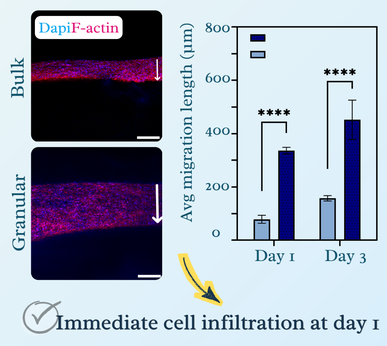
Cell encapsulation



Formation of multi-cellular organizations in granular hydrogel

A 2-fold increase in cell proliferation

Cell infiltration



Immediate cell infiltration at day 1

Up to a 3-fold increase of cell infiltration in granular hydrogel over a 3-day period

Spatial confinement of cells in void spaces → ↑ Biological performance

Conclusions

- We determined the optimal inter-and intra-crosslinking point to be at 5/3 (Unit.mL^{-1}/mM) HRP/H_2O_2 and (0.25/2.5) mM Ru/SPS.
- We determined the packing density to be at 80%.
- Embedded cells adopted an elongated morphology and formed multicellular organizations in 3D-printed scaffolds.

Future perspectives

- This platform presents a promising approach for engineering self-organized cellular structures, with potential applications in organ modeling and tissue engineering.
- Next step: Immunomodulatory effects of granular bioinks mediated by fibroblast–macrophage communication..

Acknowledgments

umcg | BBT Biomaterials and Biomedical Technology | Santos' Lab | university of groningen

Let's connect!